Gynecologic Oncology 153 (2019) 694–702

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Antibody-drug conjugates in gynecologic malignancies

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HIGHLIGHTS

- ADCs are a rapidly growing class of oncologic agents that can confer tumor-specific delivery of a cytotoxic agent.
- Mirvetuximab soravtansine is an anti-folate receptor alpha ADC currently in phase III clinical trials in ovarian cancer.
- Mesothelin, tissue factor, MUC16 (CA125), NaPi2B, and Trop2 are additional ADC targets studied in gynecologic malignancies.

ARTICLE INFO

Article history:
Received 6 December 2018
Received in revised form 16 March 2019
Accepted 18 March 2019
Available online 28 March 2019

Keywords:
Antibody-drug conjugates
Ovarian cancer
Endometrial cancer
Cervical cancer

ABSTRACT

Antibody drug conjugates (ADCs) are an exciting class of oncologic therapeutics. ADCs have been FDA approved in hematologic malignancies and breast cancer and are a growing area of study in numerous solid malignancies. The desire for tumor-specific therapies with decreased systemic toxicity has driven over a decade of research into the design and optimization of ADCs, which are now in a third generation of development. Gynecologic malignancies in particular suffer a dearth of novel therapies. This review will examine the field of ADCs in gynecologic cancers, focusing on ADCs targeting folate receptor alpha (FRα), mesothelin, tissue factor, MUC16 (CA125), NaPi2B, and Trop2.

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https://doi.org/10.1016/j.ygyno.2019.03.245
0090-8258/

1. Introduction

Antibody drug conjugates (ADCs) are a rapidly growing class of oncologic therapeutics with the potential to deliver a toxic payload to tumor cells in a specific manner, theoretically minimizing systemic toxicity while maximizing efficacy. This method of drug delivery is under intense development, with >100 active trials studying ADCs across solid and hematologic malignancies. There are currently four FDA-approved ADCs: brentuximab vedotin in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma, gemtuzumab ozogamicin for treatment of acute myeloid leukemia, inotuzumab ozogamicin for the treatment of B-ALL, and ado-trastuzumab emtansine (T-DM1) for HER2-positive metastatic breast cancer. This review will discuss the ADCs in development in gynecologic malignancies.

2. General principles of ADC design

2.1. Structure of ADCs & design considerations

ADCs are composed of an antibody, a cytotoxic payload, and a synthetic chemical linker joining the two. Each component contributes to an ADC's biodistribution, tumor specificity, and cytotoxic effects. Careful design and selection of each component is required for a clinically effective ADC. As ADCs have progressed in development, payload molecules have in some cases been standardized to be attached at precise residues, linkers have been engineered to allow for controlled release of payloads, and new payloads are being designed for novel cytotoxic effects.

2.2. Antigen/antibody

Proper selection of the antigen to which the ADC will bind is crucial. The antigen confers specificity of the ADC, and thus should be highly or preferentially expressed on the tumor cell, minimally expressed on normal tissues, and present on the cell surface to allow recognition and binding by the circulating ADC. The antigen should allow internalization of the bound ADC if the payload requires intracellular deposition.

Selection and design of the antibody is fundamental, as it is the vehicle by which a payload is brought to the tumor cell. Antibodies are composed of four polypeptides: two identical heavy chains and two identical light chains, joined by disulfide bonds. The antigen binding sites on the Fab region of the immunoglobulin, containing the complementarity determining regions, must be designed for specificity to the antigen. The heavy chain defines the class of antibody (IgA, IgD, IgE, IgG, or IgM) and the Fc region, consisting of two heavy chains, determines the associated immune effects. IgG is most commonly used in ADCs, and there are four isotypes of IgG that differ based on heavy chain amino acid sequences, number of disulfide bonds to which payloads can be attached, and immune effector functions. Table 1 summarizes IgG isotypes used in ADCs. Immunoglobulins can be engineered to allow attachment of payload molecules at specific residues on the antibody, for example, by mutation of cysteines to improve stoichiometry of payload attachments and avoid disruption of interchain disulfide bonds [1,2], or mutation of residues to alter the local electric charge, decrease unintended payload deconjugation, and improve payload stability [3]. The Fc portion of IgG1 can be engineered to abrogate its effector immune functions to reduce toxicity, generating "Fc-silent" antibodies [4], or conversely to enhance its effector functions and possible additional anti-tumor immune effects [5].

2.3. Payloads

Payloads are small-molecule drugs measuring 300–1000 Da, highly potent with nano- or picomolar IC50 values despite chemical alteration to become linkable, and relatively hydrophilic. Payloads that are too hydrophobic can cause ADC aggregation, increased immunogenicity, and faster clearance [6]. There are several classes of payload molecules used in ADCs, though the majority utilize agents in the auristatin or maytansine families [7]. Auristatins are synthetic, water soluble, highly potent analogues of dolastatin-10, a natural antimitotic drug, that inhibit tubulin assembly and thus are toxic to proliferating cells. Monomethyl auristatin E (MMAE, vedotin) can act on neighboring cells via bystander effect, as its neutral charge allows diffusion across cell membranes. Monomethyl auristatin F (MMAF, mafodotin) carries a charged carboxy-terminal phenylaline residue that prevents membrane diffusion and hence does not have a bystander effect. Maytansinoids are synthetic analogues of maytansine, a natural benzoansamacrolide, and act similarly to vinca alkaloids by binding tubulin and inhibiting microtubule assembly. DM1 maytansinoids include emtansine and mertansine; DM4 maytansinoids include soravtansine and ravtansine. Table 2 summarizes additional classes of payload molecules. Drug:antibody ratio (DAR) refers to the average number of payload molecules attached to the antibody. In general, a lower DAR may reflect a less potent ADC, whereas a higher DAR is associated with greater potency. However, depending on the characteristics of the payload molecule, a high DAR can ultimately reduce ADC efficacy by affecting biodistribution (e.g. accumulation in non-target organs), increased drug clearance, and negatively impacting antigen binding [8].

Table 1
IgG isotypes used in ADCs.

IgG isotype	Structure	Immune effector function	Additional points
IgG1	16 disulfide bonds	Antibody-dependence cell-mediated cytotoxicity (ADCC) Complement-dependent cytotoxicity (CDC)	Most commonly used in ADCs
IgG2	18 disulfide bonds Complex hinge region	Limited ADCC and CDC	
IgG4	16 disulfide bonds Complex hinge region	Limited ADCC and CDC	Can form half-antibodies (one heavy chain + one light chain) Can form bispecific antibodies via Fab arm exchange

Table 2
Major payload classes.

Class	Mechanism of Action	Example compounds
Auristatins	Inhibit tubulin assembly	MMAE (vedotin) MMAF (mafodotin)
Maytansines	Inhibit tubulin assembly	DM1: emtansine, mertansine DM4: soravtansine, ravtansine
Tubulysins	Inhibit microtubule polymerization	AZ13599185
Pyrrolobenzodiazepines (PBDs)	Bind the minor groove of DNA in a sequence-specific manner, dimerization of PBDs cause crosslinking of DNA	
Calicheamicin	Bind the minor groove of DNA, induces double-strand DNA breaks	*N*-acetyl-γ-calicheamicin
Duocarmycins	Bind the minor groove of DNA, alkylating agent	Seco-DUBA
Indolinobenzodiazepines	Bind the minor groove of DNA, alkylate only one strand of target DNA	
Camptothecin analogues	Inhibit DNA topoisomerase 1	SN-38 (the active metabolite of irinotecan) DX-8951f (exatecan mesylate)

2.4. Linker

Linkers are important modulators of overall ADC pharmacokinetics, pharmacodynamics, and toxicity, and should be selected in combination with the payload and antibody for optimal clinical effectiveness [9]. Linker design determines when and where the payload is offloaded (deconjugated). The linker should be inert enough to allow for ADC stability while in solution and circulation, as premature release of the payload prior to reaching the target cell may cause systemic toxicity. Choice of linker and coupling chemistry affects the DAR of an ADC, with issues as previously described [9]. Linkers generally fall into two classes: cleavable or non-cleavable. Cleavable linkers include motifs sensitive to enzymatic cleavage by proteases, to hydrolysis at acidic pH, or to redox reactions that occur within early or late endosomes or lysosomes. Non-cleavable linkers, such as succinimidyl 4-*N*-maleimidocaproyl used in T-DM1 (ado-trastuzumab emtansine), rely on the lysosomal proteolytic degradation of the antibody backbone to free the payload. The end product consists of a payload and any elements of the linker that are still attached. Therefore, linkers can affect the electric charge and hydrophobicity/hydrophilicity of the payload [10]. This has two effects, one of which is to affect the payload's membrane-diffusing ability, thus imparting or preventing a bystander effect on neighboring, non-antigen-expressing cells. Second, this can influence efflux of the linker-payload molecule by cellular drug efflux pumps, which more efficiently transport neutral, nonpolar compounds, thus impacting intracellular levels of the payload and possibly primary or acquired drug resistance. Though ADCs in current clinical trials utilize linkers designed for the internalization of an ADC, new linkers are in development, designed for ADCs that target non-internalizing antigens. These linkers are cleaved external to the target cell by a second-step chemical activator to allow extracellular payload release [11].

3. ADCs in gynecologic malignancies

ADCs currently in development in gynecologic cancers will be discussed, organized by ADC target (antigen) and focusing on ADCs furthest in clinical development. Table 3 summarizes all current ADCs currently being explored in gynecologic cancers. Table 4 summarizes the common antigens discussed here and the frequency of expression reported in gynecologic cancers.

4. Folate receptor alpha (FRα)

FRα, also known as folate binding protein, is a cell-surface transmembrane glycophosphatidylinositol (GPI)-anchored glycoprotein that facilitates the unidirectional transport of folate into cells. FRα is minimally expressed on normal adult tissues with polarized epithelia, including the choroid plexus, proximal tubules of the kidney, epithelium of the fallopian tubes, ovaries, uterus, and cervix, acinar cells of the breast, and type I and II pneumocytes of the lung [12]. Aberrant or high expression of FRα is seen in ovarian, endometrial, breast, and non-small cell lung cancers [13,14], and is theorized to be upregulated in response to increased folate demand, as folate is an essential co-factor for one-carbon transfer reactions required for DNA and RNA synthesis, cell growth, and proliferation.

4.1. Mirvetuximab soravtansine (IMGN853)

Mirvetuximab soravtansine is an anti-FRα ADC, utilizing a humanized IgG1 conjugated to a DM4 payload via a charged, cleavable sulfo-PDB linker. DM4 is randomly conjugated, with a DAR of 3.5:1. Mirvetuximab is metabolized to three forms of the payload, lysine-Nε-sulfo-SPDB-DM4, *S*-methyl-DM4, and DM4, all of which can inhibit tubulin and cause G2-M arrest and cell death. Additionally, *S*-methyl-DM4 is electrically neutral and lipophilic, thus able to diffuse across biomembranes and induce a bystander effect [15,16].

Mirvetuximab demonstrated clinical activity in an unselected patient population in a phase I dose-escalation trial across solid tumors, inclusive of heavily pretreated epithelial ovarian cancer (EOC) and endometrial cancer. Of 44 patients enrolled, 23 had recurrent EOC. This trial established a dose of 6.0 mg/kg adjusted ideal body weight (AIBW) every 3 weeks as the RP2D. Treatment-emergent AEs most commonly included diarrhea (34%), fatigue (32%), nausea (25%), and blurred vision (25%). SAEs included grade 3 hypophosphatemia, pulmonary edema, punctate keratitis, and corneal opacity. Ocular toxicity was reversible after cessation of therapy. Of 43 evaluable patients, there was an overall clinical benefit rate (ORR + SD ≥ 4 months + CA125 response) of 23%, including confirmed PRs in 2 patients (both EOC) for an ORR 5%, SD in 22 patients (including 2 EOC) of which 4 pts experienced SD for >4 months, and 5 patients with a confirmed CA125 response (4 with EOC, 1 with endometrial cancer) [17]. Mirvetuximab was further studied in an expansion cohort of 46 patients with platinum-resistant EOC with demonstrated FRα positivity by IHC, defined as ≥25% of tumor cells with at least 2+ staining. All had seen prior platinum and taxanes, with half receiving 1–3 lines of therapy (23 patients) and half receiving ≥4 lines (23 patients). Ocular toxicities occurred in 26% of patients, leading to study discontinuation for one patient. Analysis of all 46 treated patients demonstrated a confirmed ORR 26%, including 1 CR and 11 PR, with median PFS 4.8 months and median duration of response (DoR) of 19.1 weeks. Stratifying by number of prior therapies, a post-hoc analysis showed that patients receiving 1–3 prior lines fared better than those receiving ≥4 lines, with ORR 39% vs 13%, and median PFS 6.7 months vs 3.9 months ($p = 0.002$) [18]. While responses were seen regardless of FRα expression, a pooled analysis of the three phase I expansion cohorts ($n = 113$) showed a confirmed ORR 46% (1 CR, 16 PR) in 37 patients who met criteria for medium or high FRα expression [19]. A phase 1b expansion cohort directly evaluated this effect in medium/high expressors [20]. Patients with FRα-positive relapsed platinum sensitive or resistant EOC underwent biopsy of lesions pre- and post-treatment (after 2 cycles of mirvetuximab). FRα expression remained stable despite mirvetuximab administration and appeared to correlate with degree of response, though the small sample size precluded formal statistical analysis. In low-expressors (6 patients), there were no objective responses, with median PFS 2.8 months. In medium-expressors (5 patients), ORR 20% with median PFS 3.9 months. In high-expressors (16 patients), ORR 31% (including 2 CRs) with median PFS 5.4 months [20]. These data

Table 3
ADCs in at least phase I evaluation in gynecologic cancers.

Antibody target (Antigen)	ADC	Antibody	Linker	Payload	Gynecologic cancers under evaluation	Active trials (clinicaltrials.gov)
Folate receptor alpha (FRα)	Mirvetuximab soravtansine (IMGN853)	Humanized IgG1 (M9346A)	N-hydroxysuccinimidyl-4-(2-pyridyldithio)-2-sulfobutanoate ("sulfo-PDB")	Soravtansine	Ovarian cancer	NCT03552471 NCT02996825 NCT02606305
Mesothelin	Anetumab ravtansine (BAY 94-9343)	Fully human IgG1 (MF-T)	N-hydroxysuccinimidyl-4-(2-pyridyldithio)-2-sulfobutanoate ("sulfo-PDB")	Ravtansine	Ovarian cancer	NCT02751918 NCT03587311
	DMOT4039A (RG7600)	Humanized IgG1 (h7D9v.3)	Protease-labile valine-citrulline linker	MMAE		
	BMS-986148	Undisclosed	Undisclosed	Undisclosed	Solid malignancies, includes ovarian cancer	NCT02341625
Tissue factor	Tisotumab vedotin (HuMax-TF-ADC, or TF-011-MMAE)	Humanized IgG1	Protease-cleavable valine-citrulline linker	MMAE	Ovarian, endometrial, cervical cancers	NCT03245736 NCT03438396 NCT02001623 NCT03657043
MUC16	DMUC5754A (sofituzumab vedotin)	Humanized IgG1	Protease-cleavable maleimidocaproyl-valine-citrulline-*p*-amino-benzyloxycarbonyl linker	MMAE	Ovarian cancer	
	DMUC4064A (anti-MUC16 TDC)	Cysteine-engineered humanized IgG1	Undisclosed	MMAE	Ovarian cancer	
NaPi2B	Lifastuzumab vedotin (LIFA, or DNIB0600A)	Humanized IgG1 (MNIB2126A)	Protease-cleavable valine-citrulline linker	MMAE	Ovarian cancer	
	XMT1536	Not disclosed	Not disclosed	Auristatin-F-HPA	Ovarian cancer	NCT03319628
Trop2	Sacituzumab govitecan (IMMU-132)	Humanized IgG (RS7)	Acid-cleavable CLA2 linker	SN-38	Epithelial cancers, including ovarian and endometrial cancer	NCT01631552
	PF-06664178 (RN927C)	Engineered IgG1	Not disclosed	PF06380101, a novel auristatin	Ovarian cancer	
CD166	CX2009	Not disclosed	Not disclosed	DM4	Solid tumors, including ovarian and endometrial cancer	NCT03149549
AXL receptor tyrosine kinase	HuMax-AXL-ADC	Not disclosed	Protease cleavable linker	MMAE	Solid tumors, including ovarian, endometrial, and cervical cancer	NCT02988817
Protein tyrosine kinase-like 7 (PTK7), CCK4	PF-06647020	Not disclosed	Protease cleavable valine-citrulline linker	Auristatin-0101	Solid tumors, including ovarian cancer	NCT02222922
NOTCH3	PF-06650808	Humanized IgG1	Cleavable cysteine-reactive linker	Auristatin	Solid tumors, including ovarian cancer	
Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)	SAR408701	Not disclosed	Sulfo-PDB linker	DM4	Solid tumors, including ovarian, endometrial, and cervical cancer	NCT02187848
Lysosome-associated membrane protein-1 (LAMP1)	SAR428926	Not disclosed	Sulfo-PDB linker	DM4	Ovarian cancer	
CA6	SAR566658	IgG1	SPDB linker	DM4	Ovarian and cervical cancer	
MUC1 (CD227)	CMB-401	Engineered IgG4	Hydrazone linker	Calicheamicin	Ovarian cancer	
Cadherin-6 (CDH6)	HKT288	Fully human IgG1 (LTV977)	Sulfo-PDB linker	DM4	Ovarian cancer	
TIM-1	CDX-014	Not disclosed	Protease cleavable valine-citrulline linker	MMAE	Ovarian clear cell carcinoma	NCT02837991
Undisclosed antigen	SC003	Not disclosed	Not disclosed	Pyrrolobenzodiazepine	Ovarian cancer	NCT02539719
HER2	SYD985	Humanized IgG1 (Trastuzumab)	Cleavable valine-citrulline linker	Seco-duocarmycin hydroxybenzamide azaindole (seco-DUBA)	Solid tumors, including endometrial cancer	NCT02277717
	ARX788	Undisclosed	Para-acetyl-phenylalanine (pAcF)	MMAF	Solid malignancies	NCT02512237 NCT03255070
	A166	Undisclosed	Undisclosed	Undisclosed	Solid malignancies, includes cervical, ovarian	NCT03602079

provided the rationale for FRα thresholds in the subsequent FORWARD I and FORWARD II trials.

FORWARD I is an international phase III trial that enrolled 366 women with medium or high FRα expressing platinum resistant EOC, with 1–3 lines of prior therapy. Patients were randomized 2:1 to mirvetuximab 6 mg/kg AIBW every 3 weeks, or to investigator's choice of paclitaxel 80 mg/m^2 weekly, pegylated liposomal doxorubicin (PLD) 40 mg/m^2 every 4 weeks, topotecan 1.25 mg/m^2 days 1–5 every 3 weeks, or topotecan 4.0 mg/m^2 days 1,8,15 every 4 weeks. Accrual completed in April 2018, and top-line results were announced March 2019. Mirvetuximab demonstrated a higher ORR 22% compared to chemotherapy (ORR 12%, $p = 0.015$); however there was no statistical difference in PFS (HR 0.98, $p = 0.897$) nor OS (HR 0.81, $p = 0.248$). In the pre-specified high-FRα-expressing patients ($n = 218$), mirvetuximab resulted in a longer PFS (HR 0.69, $p = 0.049$); this was not statistically significant based on the trial design using the Hochberg procedure requiring this subset to obtain a p-value ≤ 0.025 to achieve statistical significance, in the context of a non-significant p-value of the intent-to-treat population. Similarly, in this subset, OS benefit with mirvetuximab did not reach statistical significance (HR 0.62, $p = 0.033$). Further analyses are ongoing.

Mirvetuximab was shown in preclinical models to potentiate the activity of established antineoplastic agents, such as carboplatin, PLD, and bevacizumab [21], forming the basis of the phase Ib/II FORWARD II trial of mirvetuximab in combination with bevacizumab, carboplatin, PLD, or pembrolizumab. In the dose escalation cohort of platinum sensitive patients with FRα-positive relapsed EOC treated with combination mirvetuximab + carboplatin, patients were escalated to carboplatin AUC 5 (completing at least 6 cycles) and mirvetuximab 6 mg/kg AIBW with investigator discretion for mirvetuximab maintenance [22]. Of 18 patients enrolled, there were 7 FRα low-expressors, 4 medium-expressors, and 7 high expressors. Of 17 evaluable patients, the ORR was 71%, including 3 CRs (all FRα high-expressors) and 9 PRs. Median PFS was 15 months. Evaluation of FRα medium- and high-expressors ($n = 10$) showed an ORR of 80%. Combination therapy was well-tolerated, with lower incidence of myelosuppression and alopecia compared to paclitaxel-containing regimens. One patient developed a grade 2 motor neuropathy that resolved after study discontinuation. Four patients (22.2%) developed ocular toxicity. Preliminary data from the mirvetuximab + pembrolizumab cohort in platinum-resistant EOC patients ($n = 14$) showed that 43% of patients had a confirmed PR, with median PFS 5.2 months and median DoR 30.1 weeks. Five of 8 medium- or high-expressors had responses, with median PFS 8.6 months and median DoR 36.1 weeks, prompting enrichment for medium and high FRα expressors in the expansion phase. Preliminary findings of the combined escalation and expansion cohorts ($n = 56$) demonstrated a confirmed PR in 16 patients, with additional unconfirmed PRs in 9 patients, for a confirmed ORR of 30%, median PFS 4.2 months, and median DoR 6.9 months [23]. In medium- or high-expressors, the confirmed ORR was 31%, with median PFS 5.5 months, and median DoR 8.1 months, and 16 patients were still on study at time of analysis. This suggests benefit of combination therapy over mirvetuximab monotherapy. The FORWARD II expansion cohort evaluating the triplet combination of mirvetuximab + carboplatin + bevacizumab is underway in patients with platinum-sensitive EOC.

5. Mesothelin

Mesothelin is a membrane-bound GPI-linked glycoprotein with minimal expression in non-malignant tissues, limited to normal mesothelial cells of the pleura, pericardium, and peritoneum [24]. It is overexpressed in almost all cases of mesothelioma, ovarian cancers, and pancreatic cancers, half of lung and gastric cancers, and two-thirds of triple negative breast cancers [25]. In cancer, mesothelin is involved in promotion of tumorigenesis via IL6 induction and resistance to TNFα-induced apoptosis [26], development of an invasive phenotype via induction of MMP-7 and MMP-9 [27], and enhancement of metastatic spread via adhesion of MUC16-expressing cells [28]. High mesothelin expression is correlated with a poorer prognosis in EOC [29].

5.1. Anetumab ravtansine (BAY 94-9343)

Anetumab ravtansine is an anti-mesothelin ADC, utilizing a fully human IgG1 conjugated to a DM4 maytansinoid payload with a DAR 3.2, via a charged, cleavable sulfo-PDB linker. Anetumab-bound mesothelin is degraded in lysosomes. Notably, mesothelin is resynthesized to reconstitute cell surface expression, making this a favorable ADC target [30]. Anetumab is capable of a bystander effect on mesothelin-negative cells [31].

A phase 1 dose-escalation cohort, including 4 EOC patients, established anetumab 6.5 mg/kg every 3 weeks as the maximum tolerated dose (MTD), which was used for the dose expansion cohort and included 20 EOC patients. Of 32 patients receiving the MTD, 18% had a PR and 47% achieved SD, for a DCR 65% (required SD duration not reported). Of a total of 22 EOC patients receiving the MTD, 9% achieved a PR and 50% had SD, for a DCR 59% (required SD duration not reported). Therapy was well tolerated with asymptomatic transaminitis, GI disorders, and reversible keratopathy as seen in other ADCs.

Phase 1 combination trials were based on preclinical data showing efficacy when anetumab was combined with doxorubicin, PLD, copanlisib, or bevacizumab [30]. In a phase Ib trial, patients with platinum resistant EOC were treated with a combination of anetumab ravtansine and PLD [32]. Patients in the dose escalation cohort were treated with anetumab 5.5 mg/kg or 6.5 mg/kg every 3 weeks, with PLD 30 mg/m^2, and dose expansion occurred using anetumab 6.5 mg/kg + PLD 30 mg/m^2. The most common grade 3–4 AEs were fatigue (24%), neutropenia (24%), and sudden death NOS (14%). Of a total of 21 patients, 11 patients (52%) experienced a confirmed PR and 7 patients (33%) had SD, for a DCR of 86% (required SD duration not reported). Six patients had a durable PR lasting >250 days. A randomized phase II study of bevacizumab with weekly anetumab ravtansine or weekly paclitaxel is ongoing, for patients with platinum resistant or refractory EOC (clinicaltrials.gov NCT03587311).

5.2. DMOT4039A

DMOT4039A, also known as RG7600, is an anti-mesothelin ADC, utilizing a humanized IgG1 conjugated to MMAE via a cleavable valine-citrulline linker with DAR 3.5. DMOT4039A is internalized after binding to mesothelin and trafficked to lysosomes, where linker degradation releases the MMAE payload.

A phase 1 study of DMOT4039A in patients with pancreatic or platinum-resistant EOC demonstrated safety with some antitumor activity. EOC patients were required to have a high level of mesothelin expression by IHC (3+). Thirty-one EOC patients were enrolled, having received a median of 3 prior therapies. The dose-escalation cohort determined an MTD of 2.4 mg/kg every 3 weeks, which was used for dose expansion. Grade 3/4 AEs occurred only at 2.4 mg/kg and 2.8 mg/kg dosing levels and included fatigue (9.5%), transaminitis (9.5%), neutropenia (9.5%), diarrhea (2.4%), and gastroparesis (2.4%). Cumulative peripheral neuropathy was seen in 20% of patients. Of 10 EOC patients treated at the MTD, 3 patients (30%) had confirmed PRs, with durations ranging from 2.7 to 4.1 months. Three additional patients had CA125 responses only. Median PFS was 4.9mo for all patients treated at MTD. Soluble serum mesothelin levels were assessed as an exploratory correlate but did not correlate with tumor mesothelin IHC score nor with clinical activity of DMOT4039A. There was no clear impact of pre-dose serum mesothelin levels on the pharmacokinetics of DMOT4039A.

Table 4
Expression of common antibody targets in gynecologic cancers.

Reported expression frequencies vary significantly even within a class of gynecologic malignancy. Studies employed different methods of detection (FISH, IHC, flow cytometry/FACS), evaluated or allowed different tumor histologies (e.g. low or high grade serous, endometrioid, adenocarcinoma vs squamous; histologies not consistently annotated), and employed different definitions of positivity or overexpression. Please see Supplemental Table S1 for selected references of expression frequency.

Antibody target (antigen)	Gynecologic malignancy	Expression frequency
Folate receptor alpha (Frα)	Ovarian cancer	67%–100%
	Uterine cancer	41–89%
	Cervical cancer	0–40.7%
	Gynecologic sarcomas	Not characterized
Mesothelin	Ovarian cancer	55–100%
	Uterine cancer	50–67%
	Cervical cancer	25–81%
	Uterine leiomyosarcoma	0%
Tissue factor	Ovarian cancer	23.8–100%
	Uterine cancer	100%
	Cervical cancer	94–100%
	Gynecologic sarcomas	Not characterized
MUC16	Ovarian cancer	70–90%
	Uterine cancer	65–89%
	Cervical cancer	83%
	Uterine carcinosarcoma/MMMT	0–72.7%
	Uterine leiomyosarcoma	0%
NaPi2b	Ovarian cancer	80–93%
	Uterine cancer	Not characterized
	Cervical cancer	Not characterized
	Gynecologic sarcomas	Not characterized
Trop2	Ovarian cancer	82–92%
	Uterine cancer	65–96.2%
	Cervical cancer	100%
	Carcinosarcomas	25% uterine MMMT 57% ovarian MMMT

6. Tissue factor

In humans, tissue factor (TF) is present in two isoforms, a full-length transmembrane TF (flTF) and an alternatively-spliced TF (asTF) that lacks the transmembrane domain and is soluble [33]. The membrane-bound flTF is expressed on subendothelial vessel wall cells and primarily functions in the extrinsic pathway of the coagulation cascade. Formation of a flTF:factorVIIa complex on the cell surface also initiates a protease-activated receptor 2 intracellular signaling cascade, leading to production of pro-angiogenic factors and adhesion molecules. Both flTF and asTF are implicated in cancer biology, with roles in tumor angiogenesis, cell proliferation, epithelial-mesenchymal transition, tumor escape from dormancy, metastasis, and thrombotic events [34]. Aberrant expression is seen in pancreatic, lung, prostate, breast, colon, and bladder cancers. It is aberrantly expressed in ovarian cancer but not in benign ovarian tissue [35]. Similarly, TF is aberrantly expressed in malignant cervical and uterine tissues, but not in normal cervix or endometrium [36,37].

6.1. Tisotumab vedotin

Tisotumab vedotin (Tv), also known as HuMax-TF-ADC or TF-011-MMAE, is an anti-tissue factor ADC utilizing a humanized IgG1, conjugated to MMAE via a protease-cleavable valine-citrulline peptide linker. Tv was also shown to be indirectly cytotoxic via IgG1-mediated induction of ADCC [38]. Binding of Tv to TF may prevent the subsequent downstream signaling processes that regulate angiogenesis and tumor cell proliferation.

In the Gen701 phase I/II trial of Tv in solid malignancies, including ovarian, cervical, and endometrial cancers, preliminary data from dose escalation and expansion reported epistaxis in 48% of 27 enrolled patients, including one patient who died from tumor-related bleeding [39]. This is likely due to direction competition for TF with Factor VII and partial inhibition of Factor X conversion to FXa, as seen in preclinical in vitro studies. Other common AEs included fatigue (48%), anemia (41%), alopecia (30%), nausea (30%), pyrexia (30%), abdominal pain (22%), diarrhea (22%), and constipation (30%). The RP2D was determined to be Tv 2.0 mg/kg every 3 weeks. TF expression was confirmed in 80% of samples. Tv led to 52% of patients achieving SD or better, including one cervical cancer patient who maintained a PR through the entire study period. Results from cervical cancer patients (n = 34) noted any-grade AEs of conjunctivitis (50%), epistaxis (47%), and peripheral neuropathy (35%). Any-grade ocular AEs were seen in 53% of patients, including conjunctivitis, conjunctival ulceration, and ulcerative keratitis, prompting mitigative measures including steroids, lubricating eye drops, and cooling eye masks. Tv was effective in cervical cancer, leading to an ORR of 32%, including 8 confirmed PRs and 3 unconfirmed PRs. Median DoR was 8.3 months for confirmed responses [40]. Tv is now in a phase II trial in platinum resistant ovarian cancer (clinicaltrials.gov NCT03657043). Cervical cancer trials are also being designed.

7. MUC16

MUC16 is a transmembrane mucin, which releases soluble CA125 when cleaved extracellularly [41]. It normally functions as part of a protective mucus layer on epithelial surfaces, where it is expressed at a low level [42]. MUC16 is overexpressed in pancreatic, lung, ovarian, and endometrial cancers. It is implicated in attenuating tumor cell apoptosis [43], shielding tumor cells from immune attack [44], and enhancing tumor cell invasion, adhesion, and metastasis through binding of mesothelin [28,45].

7.1. DMUC5754A

DMUC5754A, also known as sofituzumab vedotin, is an anti-MUC16 ADC utilizing a humanized IgG1 conjugated to an MMAE payload via a cleavable maleimidocaproyl-valine-citrulline-*p*-aminobenzyloxycarbonyl linker.

In a phase I trial of DMUC5754A in platinum resistant EOC or unresectable pancreatic cancer [46], patients were pre-screened for MUC16 IHC expression on archival tumor or met the surrogate criteria of an elevated serum CA125 at least 2 times the upper limit of normal. Patients were treated on a dose escalation schedule of DMUC5754A given every 3 weeks, and subsequently in a separate escalation cohort of weekly dosing. Of 77 patients treated, 66 had platinum-resistant EOC and 11 had pancreatic cancer. Forty-four of the EOC patients were treated on the every-3-week schedule, with a median of 4 prior lines of therapy. Twenty-two of the EOC patients were treated in the subsequent weekly-dosing cohort, having received a median of 5 prior lines of therapy. The RP2D was determined to be 2.4 mg/kg every 3 weeks or 1.4 mg/kg weekly. It was well tolerated, with common all-grade AEs including fatigue (57% with 3-week dosing; 30% with 1-week dosing), peripheral neuropathy (34%; 18%), nausea (34%; 46%), vomiting (27%; 36%), decreased appetite (25%; 18%), and alopecia (18%; 23%). SAEs included small bowel obstruction, hypocalcemia, and one case of posterior reversible leukoencephalopathy syndrome (PRES) in a patient recently treated with bevacizumab. Of all EOC patients with evaluable tumor samples, 16% had MUC16 IHC 2+, and 64% were IHC 3+, bearing in mind the EOC dose expansion cohort was enriched for IHC 2+/3+ expression.

EOC responders included 1 confirmed CR, 6 confirmed PRs, 2 unconfirmed PRs, and 6 with SD lasting >6 months. All EOC responders had MUC16 expression of 2+ or 3+ by IHC. In evaluating serologic response, a more stringent threshold for CA125 response of ≥70% reduction was used, as DMUC5754A binds CA125. Using this criterion, a response rate of 25% (7 of 29 patients) was seen. This trial also explored

the use of HE4 as a surrogate marker of treatment response. Using a ≥40% reduction in HE4 as a threshold for response, HE4 correlated with radiographic response, and demonstrated an HE4 response rate of 22% (5 of 23 patients).

7.2. DMUC4064A

DMUC4064A is an anti-MUC16 thiomab-ADC, termed a TDC, utilizing a cysteine-engineered humanized IgG1 conjugated to an MMAE payload. The engineered antibody allows for site-specific conjugation of 2 molecules of MMAE per antibody, providing a consistent DAR.

DMUC4064A was studied in a phase I trial in platinum resistant EOC and unresectable pancreatic cancer. Data from the dose escalation cohort of 44 enrolled patients treated at doses of 1.0 mg/kg to 5.6 mg/kg every 3 weeks suggested that it was well tolerated and safe [47]. Common AEs across dose levels included fatigue (34%), nausea (32%), diarrhea (23%), abdominal pain (21%), and ocular toxicities including keratitis (4.5%), blurred vision (9%), and dry eyes (2%). Levels of MMAE were not affected by circulating CA125. Clinical activity of DMUC4064A was seen at doses >3.2 mg/kg and included 1 confirmed CR and 6 confirmed PRs. All responders were MUC16 IHC 2+/3+.

The dose expansion cohort used a dose of 5.2 mg/kg every 3 weeks, and preliminary data from 22 enrolled patients suggests that response can be significant. AEs were similar to those in the dose escalation cohort. Ocular toxicity occurred in 15 patients, of whom 13 experienced at least one grade 2 or 3 event. Lubricating drops, steroid drops, and dose reductions were used to good effect. Four patients discontinued treatment due to grade 2 neuropathy. The confirmed ORR was 45%, including 1 CR and 8 PRs. Five of the responses exceeded a 75% reduction in tumor burden. Median PFS was 5.8 months, with a median DoR of 4.4 months. Of 8 responders with evaluable archival tumor tissue, all were MUC16 IHC 2+/3+.

8. NaPi2b

NaPi2B is a multi-transmembrane type II sodium-dependent phosphate transporter within the SLC34 solute carrier family. It functions in the transport of inorganic phosphate transcellularly and plays a role in phosphate homeostasis. Normally, it is expressed on the apical surfaces of epithelial cells, including type II pneumocytes in the lung, intestinal epithelium, and epithelial lining of the uterus and fallopian tubes [48]. It is aberrantly overexpressed in 80–90% of ovarian cancers, nonsquamous NSCLC, and papillary thyroid cancers [49].

8.1. Lifastuzumab vedotin

Lifastuzumab vedotin (LIFA, or DNIB0600A), is an anti-NaPi2B ADC utilizing a humanized IgG1 conjugated to an MMAE payload via a cleavable valine-citrulline linker.

Preliminary data from a phase I dose escalation and expansion study of LIFA suggest this ADC is well tolerated with evidence of clinical efficacy [50]. Thirty patients with platinum resistant EOC and 43 patients with NSCLC were enrolled. EOC patients were heavily pretreated, with a median of 5 prior lines of therapy. Patients received LIFA at escalating doses of 1.8 mg/kg to 2.8 mg/kg, and dose expansion occurred at 2.4 mg/kg. Common AEs included fatigue (55%), decreased appetite (34%), nausea (40%), vomiting (26%), peripheral neuropathy (36%), and alopecia (19%). Grade 3 and 4 AEs included neutropenia (8%), anemia (3%), neuropathy (3%), pneumonia (3%), hyperglycemia (1%), hyperkalemia (1%), hypertension (1%), transaminitis (1%), and upper respiratory tract infection (1%). At a dose of 2.4 mg/kg, 7 of 17 ovarian cancer patients (41%) with NaPi2B IHC 2+/3+ expression had confirmed PRs. Median DoR ranged from 1.4 to 9.4 months at time of data censoring. No responses were seen in patients with absent NaPi2B expression (IHC 0).

LIFA was compared to pegylated liposomal doxorubicin (PLD) in platinum resistant EOC in a subsequent phase II study [51]. Ninety-five patients were randomized 1:1 to LIFA given at 2.4 m/kg every 3 weeks or PLD 40 mg/m2 every 4 weeks, stratified by platinum free interval (<3 months vs 3–6 months), number of prior platinum-containing regimens (<2 vs ≥2), and number of regimens for treatment of platinum resistant disease (0 vs 1–2). Ninety-three percent of patients had NaPi2B IHC 2+/3+ expression, balanced between the LIFA (89%) and PLD (90%) arms. BRCA mutation carriers were also balanced between the arms (11% LIFA, 10% PLD). In the intent to treat population, patients treated with LIFA demonstrated an ORR of 34% (including 1 CR and 15 PR), median PFS 5.3 months, and median DoR 5.5 months. In comparison, patients treated with PLD demonstrated an ORR of 15% (including 1 CR and 6 PR), median PFS 3.1 months, and median DoR 3.9 months. There were increased rates of abdominal pain, diarrhea, and neutropenia with LIFA, but less constipation, stomatitis, and palmar-plantar erythrodysesthesia. Notably, though the ORR difference between LIFA and PLD was statistically significant ($p = 0.03$), the difference in PFS was not statistically significant. This mirrors the results from the FORWARD I trial of anti-FRα ADC mirvetuximab soravtansine and raises the question of whether response rate to ADCs consistently translates to durable clinical activity.

9. TROP2

Trop2, also known as trophoblast antigen 2 or epithelial glycoprotein-1, is a surface transmembrane glycoprotein that binds several ligands, including claudin-1, claudin-7, and cyclin D1, transducing signals for cell proliferation and survival. It is found on some normal tissues, but is overexpressed in nearly all cervical cancer and endometrioid endometrial adenocarcinomas, and more than half of uterine serous carcinomas and EOCs. Trop2 is thought to promote tumor cell proliferation, epithelial-mesenchymal transition, invasion, and metastasis [52].

9.1. Sacituzumab govitecan

Sacituzumab govitecan, also known as IMMU-132, is an anti-Trop2 ADC utilizing a humanized IgG conjugated to SN38, the active metabolite of irinotecan, via a cleavable CLA2 linker. SN38 is considered a moderately toxic payload with nanomolar potency thus requiring a higher DAR of 7.6. Conjugation of SN38 to the antibody renders it nontoxic in systemic circulation and resistant to inactivating glucuronidation.

A phase I trial enrolled 25 patients irrespective of Trop2 expression, and included 1 patient with EOC [53]. The majority of patients had pancreatic ductal carcinoma. Sacituzumab govitecan was safe, with common all-grade AEs including fatigue (72%), nausea (68%), alopecia (52%), diarrhea (52%), neutropenia (56%), vomiting (40%), and dysgeusia (20%). There was indication of efficacy, as 16 patients had SD and 3 PRs (1 small cell lung cancer, 1 triple negative breast cancer, and 1 colon cancer). Notably, of 9 patients receiving prior anti-topoisomerase-1 agents, 2 had reductions of 28% and 38% respectively in target lesions, and 5 had SD. Median time to progression overall was 3.6 months. The single patient with EOC had received 3 prior lines of therapy, with median time to progression of 1.4 months.

A subsequent dose expansion trial was conducted across 178 patients with epithelial cancers, including 1 endometrial cancer patient (8 prior lines of therapy) and 4 EOC patients (median 6 prior lines) [54]. Of 150 evaluable tumor samples from all patients, 93% were positive for Trop2 by IHC, with 82% IHC 2+/3+. Three EOC samples were 3+. Patients were treated at a dose of 8 mg/kg, then at 10 mg/kg which was selected as the RP2D. The side effect profile was notable for a higher incidence of neutropenia at 10 mg/kg. Baseline uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) was collected, and there was no correlation between the three haplotypes (*1*1, *1*28, or *28*28) and incidence of severe neutropenia, but there was a correlation between haplotype and grade 3 diarrhea across dosing levels. The

patient with endometrial cancer (uterine serous carcinoma) achieved a 66% reduction in target lesions and had continued clinical response at time of data censoring [55]. Notably she was treated at 10 mg/kg and had 3+ IHC expression of Trop2 in >90% of tumor cells.

10. Mechanisms of ADC resistance

Why some tumors are primarily resistant to ADCs or acquire resistance after a period of response remains an area of active investigation, particularly as increasing numbers of ADCs are in development. Mechanisms of resistance are coming to light, predominantly generated from preclinical models of acquired-resistance cell lines or tumors, and are dependent largely on the structure and function of the ADC [56].

There are several pharmacokinetic reasons for resistance. There may be premature payload deconjugation prior to antigen binding, leading both to systemic toxicity and decreased tumor-specific efficacy. There may be person to person variability in tissue distribution, metabolism of the ADC, and plasma clearance. Tumor vascularity is one factor dictating the amount of ADC that reaches the tumor, which can change as a tumor matures or responds to preceding therapies.

The tumor itself may inherently have, or evolve, characteristics rendering it resistant to an ADC. Heterogeneous antigen expression intratumorally may spare antigen-negative tumor cells if an ADC lacks bystander effects. Antigens may be altered, through down-regulation, truncation, or epitope mutation that impairs ADC binding [56]. As ADC processing by internalization and appropriate intracellular trafficking is required for eventual release of the payload, development of alterations in signaling or cytoskeletal molecules that affect endosome or lysosome trafficking can affect appropriate degradation of the ADC and subsequent effectiveness [57]. Within lysosomes, there can be decreased proteolytic activity, and hence decreased linker cleavage [58]. There may also be alterations in transport proteins, such as SLC46A3, that normally facilitate efflux of the free payload from lysosomes into the cytoplasm, where it can exert its cytotoxic effects [59].

As with all cytotoxic agents, as with traditional chemotherapeutic agents, resistance to ADCs may arise from alterations in the intended target of the payload. For example, tubulin mutations or isotype changes are mechanisms of resistance to taxanes and vinca alkaloids [60]. The tumor cell may further upregulate anti-apoptotic proteins to reduce its sensitivity to a cytotoxic payload. There may also be inherently high expression of or upregulation of drug efflux pumps, such as MDR1 and MRP1, reducing intracellular payload concentration to ineffective levels.

11. Conclusion

ADCs harbor significant potential for the targeted delivery of cytotoxic drugs with decreased systemic toxicity. Much work remains to be done in identifying novel tumor-specific antigens and optimizing ADC design in gynecologic malignancies. The gynecologic malignancy-focused ADCs discussed above have demonstrated efficacy as monotherapy but should also be considered in combination regimens. For example, replacement of a taxane in doublet regimens (e.g. carboplatin and paclitaxel) by an anti-mitotic ADC may demonstrate similar efficacy with less toxicity, possibly precluding dose reductions, delays, or premature termination of therapy. Combinations with immune checkpoint-blockade agents also offer the potential for durable responses and bear further investigation. Patient selection must be optimized regarding antigen expression, to maximize possible ADC effect. Careful consideration should be made to pair a payload's mechanism of cytotoxicity to genetic alterations harbored by the tumor for synergistic cell killing, for example pairing PBD payloads with *BRCA* mutation carriers in ovarian cancer. A notable point highlighted in the results of trials evaluating mirvetuximab soravtansine and lifastuzumab vedotin is the discrepancy between an improved ORR with use of the ADC, without a clear PFS benefit. Whether this reflects selective pressure accelerating growth of an ADC-resistant tumor population that abrogates any survival benefit is a possibility but remains unknown. This underscores the importance of obtaining post-progression biopsies to evaluate mechanisms of resistance. Though there is much to learn about the optimal design and application of ADCs, this class of agents has expanded the repertoire of therapeutics in gynecologic oncology and offers the potential for improved survival and quality of life.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.245.

Conflict of interest statement

EKL declares no conflicts of interest. JFL declares advisory board participation for AstraZeneca, Tesaro, Clovis, and Mersana Therapeutics, and also is or has been the institutional PI on industry-sponsored trials from Genentech/Roche, AstraZeneca, Boston Biomedical, Atara Biotherapeutics, Acetylon, Bristol-Myers Squibb, Agenus, CytomX Therapeutics, Regeneron, Tesaro, and Clovis Oncology.

Author contribution

Both authors contributed to the conception and writing of this review and gave final approval of the manuscript.

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